REMARKS/ARGUMENTS

Claims 1, 6 and 7 are pending in the current application. Claims 1 and 6 have been amended. Support for the amendments may be found throughout the specification and in the original claims. No new matter is added.

If Claims 1, 6 and/or 7 are found to be allowable, Applicants respectfully request rejoinder of the withdrawn process Claims 11, 12 and 14 that are dependent from and incorporate all of the limitations of the product claims. M.P.E.P. § 821.04(b).

Request for Withdrawal of Finality of Rejection

Applicants respectfully submit that the Finality of the Rejection dated 6 Feb. 2008 is premature, because the Examiner entered a new ground of rejection under 35 USC 103(a) which was not necessitated by Applicants' amendments to the claims.

As stated in M.P.E.P. § 706.07(a), a second or subsequent action on the merits should not be made final if the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c).

Applicants' 9 Nov. 2007 amendments to independent Claim 1 (a) incorporated the subject matter in previously presented Claim 5, strain CU-385, and (b) provided for a specific strain from which the bleb preparation that is not deficient in Por A is derived, strain B:4:P1.7b,4, Exemplified in Example 8 of Applicants' specification. The amendment which incorporated the subject matter of Claim 5 merely incorporated previously claimed subject matter into Claim 1; therefore, it did not necessitate a new search. The amendment to incorporate strain B:4:P1.7b,4 included subject matter encompassed by the previously presented claim and which should reasonably have been expected to be claimed, as it was expressly disclosed in Example 3 of Applicants' specification. Therefore, this subject matter should have been encompassed in the Examiner's previous search, and the Office Action should not have been made Final. M.P.E.P. § 706.07(a) and § 904.03. The Examiner had previously cited both Berthet *et al.* (PCT Publication WO 01/09350, 2/8/2001) and Granoff *et al.* (PCT Publication WO 02/09643, 2/7/2002) in his rejections.

Withdrawal of the Finality of the present Office Action is requested.

Claim Objections

Claims 1, 6 and 7 were objected to because of the following informality: claim 1 recites the serosubtype "B:4:P1.7,b,4." The comma immediately after the 7 should be removed so that the serosubtype is "B:4:P1.7b,4." Applicants have so amended Claim 1 and respectfully request withdrawal of this objection.

Claim Rejections Maintained

35 U.S.C. 112

Claims 6-7 were rejected under 35 USC 112, first paragraph, because the specification, while being enabling for multivalent vaccines providing protection against *Neisseria meningitidis* diesease, does not reasonably provide enablement for multivalent vaccines for protection against neisserial disease. Applicants have amended Claim 6, from which Claim 7 depends. Applicants respectfully requests withdrawal of this rejection.

New Claim Rejections

35 U.S.C. 103: Rejection over Berthet et al. in view of Vermont et al. and Baker et al.

Claims 1, 6 and 7 were rejected under 35 USC 103(a) as being unpatentable over Berthet *et al.* (PCT Publication WO 01/09350, 2/8/2001) in view of Vermont *et al.* (Infect. Immun., 70:584-590, 2/2002) and Baker *et al.* (J. Paediatr. Child Health, 37:S13-S19, 2001). Applicants respectfully traverse this rejection.

The Supreme Court has stated that the *Graham* factors continue to define the inquiry that controls in determining if the claimed subject matter is obvious under § 103. *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.* (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least the reason that the Examiner has failed to establish a rational underpinning to support the legal conclusion of obviousness based on the *Graham* factors.

To reject claims based on the rationale of combining prior art elements according to known methods to yield predictable results, the Examiner must articulate:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

72 Fed. Reg. 57526, 57529 (October 10, 2007).

(a) No motivation to combine the cited references:

One of ordinary skill in the art would not have been motivated to prepare a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA and a second bleb preparation that is not deficient in Por A.

Berthet *et al.* sought to provide methods to optimize bleb vaccines by **deleting** immunodominant variable outer membrane proteins, such a PorA (for example, page 12, lines 7-21, 24-30; page 31, lines 12-13; page 48, Example 3, lines 1-15), while Vermont *et al.* examined PorA-based meningococcal OMV vaccine responses against serosubtypte P1.7-2,4 in toddlers (page 585, Vaccine and Subjects). Therefore, one would not have been motivated to combine a vaccine which sought to delete PorA with one that was PorA specific. Each is seeking an opposite response, one to delete an immunodominant protein, the other to maintain an immunodominant protein. Therefore, one of ordinary skill would not have been motivated to produce the presently claimed combination.

Baker *et al.* does not remedy the deficiencies of Berthet *et al.* and Vermont *et al.*. Baker *et al.* only discusses the potential value of a P1.7b,4 PorA specific vaccine in controlling New Zealand's meningococcal disease epidemic; Baker *et al.* do not disclose or suggest how to make such a vaccine, only that efforts are being made to develop such a vaccine.

Additionally, notwithstanding that one of ordinary skill in the art would not have been motivated to combine the elements as claimed by known methods, the results of the combination were not predictable.

For the Examiner's convenience, Applicants submit concurrently herewith, the 23 August 2003 letter in response to the PCT Written Opinion referred to in the International Preliminary Examination Report which includes data showing the technical contribution to the art of the bleb preparations of the present invention.

(b) The cited art does not include each claimed element:

Further, the cited art does not include each element as claimed by Applicants. It does not disclose or suggest a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain, and a second bleb preparation that is not deficient in PorA, wherein the second bleb preparation is derived from *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand.

Berthet *et al.* do not disclose a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain.

First, the bleb preparations of Bethet *et al.*'s invention are from a single modified strain in which one or more of their processes is used (for example, page 35 lines 1-14, lines 17-30).

Secondly, Berthet *et al.* teach away from using a CU-385 strain as a meningococcal B bleb preparation strain. Berthet *et al.* suggest that their immunoprotective meningococcal B bleb production strain has a different PorA type than the heterologous strains against which immunoprotection is measured. The 5 heterologous strains preferred for meningococcal B are: H44/76, M97/252078, BZ10, NGP165 and CU385 (page 35, lines 20-30). Finally, page 36, lines 5-28, as cited by the Examiner, does not discuss multivalent bleb preparations of the invention, but instead provides for the use of wild-type meningococcus B bleb preparations from 2 or more strains or a meningococcus B bleb preparations of the invention as an envisaged combination with meningococcal polysaccharides. As a further distinction,

Applicants' multivalent composition does not require additional meningococcal polysaccharides to provide satisfactory Serum Bactericidal Activity.

In summary, Berthet *et al.* do not disclose a multivalent bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain; Berthet *et al.* actually teach away from using CU-385 as a meningococcal B bleb production strain; when use of more than one bleb is discussed in Berthet *et al.* it is in the context of wild-type strains in combination with polysaccharides. Therefore, Berthet *et al.* not only differs from the instant invention in that they do not disclose a composition that comprises blebs from CU-385 in combination with blebs from a *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand (page 6 Office Action), they teach away from use of CU-385 in as an immunoprotective meningococcal B bleb production strain.

Vermont *et al.* nor Baker *et al.* make up for the deficiencies of Berthet *et al.* Vermont *et al.* only evaluate the avidity maturation and IgG isotype distribution of antibodies after vaccination with a monovalent meningococcal B OMV (serosubtype P1.7-2,4) (abstract). Baker *et al.* only discusses the potential value of a P1.7b,4 PorA specific vaccine in controlling New Zealand's meningococcal disease epidemic; Baker *et al.* do not disclose how to make such a vaccine, only that efforts are being made to develop such a vaccine.

Therefore, Vermont *et al.* and Baker *et al.* also fail to disclose a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain, and a second bleb preparation that is not deficient in PorA, wherein the second bleb preparation is derived from *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness for at least the reason that Berthet *et al.* in view of Vermont *et al.* and Baker *et al.* do include each of the claim limitations.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for Claim 1 over Berthet *et al.* in view of Vermont *et al.* and Baker *et al.* The cited art does not include each element claimed, one of ordinary skill in the art would not

have combined the elements as claimed by known methods, and the results of the combination were not predictable.

Applicants respectfully submit that Claim 1 is patentable over Berthet *et al.* in view of Vermont *et al.* and Baker *et al.* Claims 6 and 7 depend directly or indirectly from patentable independent Claim 1. For at least this reason and without acquiescing in the Office Action's separate rejection of these dependent claims, Applicants respectfully submit that Claims 6 and 7 are also patentable. Accordingly, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. 103: Rejection over Granoff et al. in view of Vermont et al. and Baker et al.

Claims 1, 6 and 7 were also rejected under 35 USC 103(a) as being unpatentable over Granoff *et al.* (PCT Publication WO 02/09643, 2/7/2002) in view of Vermont *et al.* (Infect. Immun., 70:584-590, 2/2002) and Baker *et al.* (J. Paediatr. Child Health, 37:S13-S19, 2001). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Examiner has failed to establish (1) that the cited art discloses each element claimed, (2) that in combination each element would have performed the same function as it did separately, and (3) that the results of the combination were predictable.

(a) No motivation to combine the cited references:

One of ordinary skill in the art would not have been motivated to prepare a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA and a second bleb preparation that is not deficient in PorA. Granoff *et al.* sought to elicit an immune response that was broadly reactive with diverse *Neisseria meningitidis* strains and circumvent the problem of immunodominance of antigenically variable domains of PorA in vesicle or PorA-based vaccines with its OMV vaccine (for example, page 5, lines 19-25; page 14, line 32 - page 15, line 3). Vermont *et al.* examined PorA-based meningococcal OMV vaccine responses against serosubtypte P1.7-2,4 in toddlers (page 585, Vaccine and Subjects) and Baker *et al.* discussed efforts to obtain a P1.7b,4 PorA-specific vaccine to control New Zealand's epidemic.

One of ordinary skill in the art would not have been motivated to combine a vaccine which sought to **circumvent** the problem of immunodominant domains of PorA with a vaccine that was **PorA specific**. Each is seeking an opposite response, one to elicit an immune response to antigens and epitopes that are not typically immunodominant (Ganoff *et al.* page 27, lines 23-29), the other to elicit a response to a PorA-specific antigen. Therefore, one of ordinary skill would not have been motivated to combine the elements as claimed.

Additionally, the results of the combination were not predictable. As discussed above, Applicants submit concurrently herewith the 23 August 2003 letter in response to the PCT Written Opinion which includes data showing the technical contribution to the art of the bleb preparations of the present invention.

(b) The cited art does not include each element as claimed:

The cited art does not include each element as claimed by Applicants. It does not disclose or suggest a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain, and a second bleb preparation that is not deficient in PorA, wherein the second bleb preparation is derived from *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand.

Granoff *et al.* do not disclose a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain, nor does it describe a multivalent meningococcal bleb composition comprising a second bleb preparation that is not deficient in PorA, wherein the second bleb preparation is derived from *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand. First, Granoff relates to immunization with blebs of three specific strains, RM1090, BZ198 and Z1092, each of which is selected from a different serotype. That is, RM1090 is a *N. meningitidis* C strain (C:2a:P1.5,2:L3,7); BZ198 is a *N. meningitidis* B strain (B:NT:P1.4); and Z1092 is a *N. meningitidis* A strain (A:4,21:P1.10). None of the strains administered by Granoff *et al.* is CU-385, and none of the strains is a *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand.

Secondly, not only do Granoff *et al.* fail to exemplify use of CU-385, they also do not suggest that CU-385 be used in their vaccine. The Examiner states that CU-385 is referred to

on page 14 and Figure 1. However, on page 14 and Figure 1 Granoff *et al.* merely provide a summary of results from different vaccine efficacy trials; there is no suggestion that the single bleb OMV vaccine referred to on page 14 and Figure 1 be used in a multivalent vaccine as defined by Applicants (page 3, lines 25-27, as a composition comprising at least 2 different blebs).

Finally, Granoff *et al.* point towards the sequential administration of different OMVs (page 6, lines 23-31; page 7, lines 19-27, as cited by the Examiner, page 23 line 19 – page 25, line 8), also discussed in the enclosed Response to the Written Opinion, 23 August 2003, not to a single administration. In its brief reference to mixtures, Granoff *et al.* also points towards sequential administration, an initial administration of a mixture which can be followed by one or more additional sequential administrations (for example, page 6, lines 23-25; page 25, lines 9-22).

In summary, Granoff *et al.* do not disclose administration of a multivalent meningococcal bleb composition comprising CU-385 nor a *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand; they do not suggest use of either CU-385 nor a *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand; they actually point to sequential administration of OMVs versus a single administration of a multivalent vaccine.

Vermont *et al.* nor Baker *et al.* make up for the deficiencies of Granoff *et al.* As discussed above, Vermont *et al.* only evaluate the avidity maturation and IgG isotype distribution of antibodies after vaccination with a monovalent meningococcal B OMV. (serosubtype P1.7-2,4) (abstract).

Baker *et al.* only discusses the potential value of a P1.7b,4 PorA specific vaccine in controlling New Zealand's meningococcal disease epidemic; Baker *et al.* do not disclose how to make such a vaccine, only that efforts are being made to develop such a vaccine.

Therefore, Vermont *et al.* and Baker *et al.* also fail to disclose a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from the *Neisseria meningiditis* B CU-385 strain, and a second bleb preparation that is not deficient in PorA, wherein the second bleb preparation is derived from *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness for at least the reason that Granoff *et al.* in view of Vermont *et al.* and Baker *et al.* do not include each of the claim limitations.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for Claim 1 over Granoff *et al.* in view of Vermont *et al.* and Baker *et al.* The cited art does not include each element claimed, one of ordinary skill in the art would not have combined the elements as claimed by known methods, and the results of the combination were not predictable.

Applicants respectfully submit that Claim 1 is patentable over Berthet *et al.* in view of Vermont *et al.* and Baker *et al.* Claims 6 and 7 depend directly or indirectly from patentable independent Claim 1. For at least this reason and without acquiescing in the Office Action's separate rejection of these dependent claims, Applicants respectfully submit that Claims 6 and 7 are also patentable. Accordingly, Applicants respectfully request that this rejection be withdrawn.

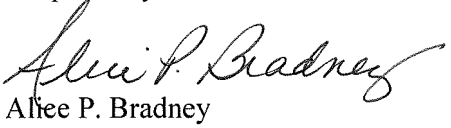
35 U.S.C. 112

Claims 1, 6 and 7 were rejected under 35 USC 112, second paragraph, as being indefinite. Applicants have amended Claim 1 to make clear that the first bleb preparation is derived from *Neisseria meningitidis* B CU-385 and the second bleb preparation is derived from *Neisseria meningitidis* B:4:P1.7b,4. Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants submit that the present application is in condition for allowance. Should any outstanding issues remain, the Examiner is encouraged to contact Applicants' undersigned representative directly by telephone.

Respectfully submitted:



Allee P. Bradney
Attorney for Applicants
Reg. No. 51,491

Date: *April 7, 2008*
GlaxoSmithKline Inc.

Corporate Intellectual Property
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
Tel. (919) 483-1891
Fax: (919) 483-7988

GlaxoSmithKline

Corporate Intellectual Property

GlaxoSmithKline Services Unlimited
980 Great West Road
Brentford
Middlesex
TW8 9GS
Tel +44 (0)20 8047 5000
www.gsk.com

European Patent Office
D-80298 Munchen
Germany

Direct tel 020 8047 4434
Direct fax 020 8047 6894
E-Mail Michael.J.Lubienski@GSK.Com

23 August 2003

Our ref MJL/B45308 PCT
Your ref .

Please quote our reference on all correspondence

VIA AIRMAIL and FACSIMILE
Fax No. 00 49 89 2399 4465

Dear Sirs,

Re: Written Opinion on PCT/EP03/06094
in the name of GlaxoSmithKline Biologicals S.A. and Instituto Finlay

After speaking to the Examiner over the phone it was decided that applicant would introduce data to show the beneficial technical contribution to the art of the bleb preparations of the present invention. I enclose said human clinical data.

Secondly, the Examiner pointed out the mention of strain CU-385 in document D1. In this regard it should be noted that D1 only mentions this strain as a reference strain to test the sera of the examples generated with different strains (which are not deficient in PorA). On top of not mentioning the beneficial effect of using an OMV in a bleb mixture which is deficient in PorA, D1 also points towards sequential administration of different OMVs (rather than mixtures) as being the preferred embodiment. For instance, at the bottom of page 48 and Figure 8 it is stated that sequential administration was better than mixing different blebs in terms of bactericidal activity against strains CU-385 and 1000.

We would therefore submit that D1 does not provide motivation for mixing a bleb preparation that is deficient in PorA with one that is not deficient.

Yours faithfully,

Michael J. Lubienski
Authorised Representative

Clinical Trial MenB-002

Subjects aged between 12 to 18 years old (n=150 per group) were immunized with a bivalent MenB OMV vaccine (comprising 25μg of each bleb derived from strain CU-385 (B:4:P1.15,19) and NZ-228/98 [a New Zealand epidemic strain B:4:P1.7b,4]) by intramuscular route using two different immunization schedules (0-2-4 months; 0-1-6 months), or with Havrix-Meningitec-Havrix (0-1-6 month immunization schedule) as control (Havrix is a Hepatitis A vaccine, Meningitec only protects against MenC strains). The bactericidal antibody titers to serogroup B Neisseria meningitidis strains were determined using serum bactericidal assays (SBA) using human complement in preimmune (Pre), one month post second injection (P II) and one month post third injection (P III) sera. Responders in P II and P III were defined as subjects with a 4-fold increase in bactericidal antibody titers in post II and post III as compared to titer in Pre sera, respectively. At the PorA serosubtype level, the M687 strain is homologous to the P1.15 OMV, the NZ124 strain is homologous to the P1.4 OMV, while the other strains (B16B6, BZ10, H44/76) are heterologous to the vaccine OMVs. The vaccine gives good homologous protection against the endemic New Zealand strain, but also protects against heterologous strains due to the presence of CU-385 blebs which are deficient in PorA.